



# The National Center for Post-Traumatic Stress Disorder

## PTSD RESEARCH QUARTERLY

VOLUME 14, NUMBER 4

ISSN 1050-1835

FALL 2003

### EMERGING NEUROBIOLOGICAL FACTORS IN STRESS RESILIENCE

Steve M. Southwick, MD<sup>1</sup>Charles A. Morgan, MD<sup>2</sup>*National Center for PTSD and  
Yale University School of Medicine*Meena Vythilingam, MD<sup>3</sup>*National Institute for Mental Health*John H. Krystal, MD<sup>4</sup>*National Center for PTSD and  
Yale University School of Medicine*Dennis S. Charney, MD<sup>5</sup>*National Institute for Mental Health*

To date, clinical neurobiological research in stress and trauma has primarily focused on stress-related disorders such as PTSD. While these studies have contributed greatly to our understanding of the pathophysiology and treatment of stress-related disorders, relatively little attention has been paid to neurobiological factors that potentially convey protection and/or promote resilience in the face of stress and trauma. By studying animals and humans who have adapted well to highly adverse conditions, researchers have recently begun to identify a neurochemical profile that characterizes resilient individuals and that may, in the future, help to predict who will develop psychiatric symptoms in response to traumatic stress versus who will rebound rapidly or even benefit from their challenging experiences.

In this review we briefly discuss a number of neurotransmitters, neuropeptides, and hormones that are known to be altered by psychological stress and that functionally interact with neural circuits thought to be related to resilience, including circuits involved in the regulation of reward, fear conditioning, and social behavior. Ten neurochemicals are highlighted, although numerous others are undoubtedly also relevant to the emerging neurobiology of resilience (Charney, in press; 2003).

During situations of danger, the sympathetic nervous system (SNS) releases epinephrine and norepinephrine (NE) in order to protect the organism. The magnitude of sympathetic nervous system responses to stress and danger varies from one person to the next. Some people have an unusually robust SNS response to stress and in essence "over-react." Unchecked persistent SNS hyper-responsiveness may contribute to chronic anxiety, hypervigilance, fear, intrusive memories, and increased risk for hypertension and cardiovascular disease. Such responses have been

found in individuals diagnosed with PTSD (Southwick et al., 1999). In contrast, it is likely that psychologically resilient individuals maintain SNS activation within a window of adaptive elevation, high enough to respond to danger but not so high as to produce incapacity, anxiety, and fear (Charney in press; Morgan et al., 2000). Dienstbier (1989) has reviewed a series of studies showing that high chronic levels of epinephrine may be associated with chronic feelings of stress. On the other hand,

#### VA Readers:

*Please see Page 7 for important information about your subscription.*

enhanced performance and emotional stability has been associated with a pattern of relatively low baseline epinephrine and robust spikes in epinephrine during challenging situations followed by rapid returns to baseline. One neurochemical that helps to maintain SNS activity within an optimal window or range is neuropeptide Y (NPY), an amino acid that is released with norepinephrine when the SNS is strongly activated (Southwick et al., 1999). One of NPY's actions is to inhibit the continued release of NE so that the SNS does not "overshoot." Preliminary studies in highly resilient special operations soldiers (Special Forces) have shown that high levels of NPY during extreme training stress are associated with better performance (Morgan, Wang, Mason et al., 2000; Morgan, Wang, Southwick et al., 2000). In these soldiers, robust increases in norepinephrine are held in check by

*PILOTS Database moves to new host, adds enhanced searching and output!*

*See Special Pull-Out Guide.*

similarly robust increases in NPY. In contrast, among traumatized combat veterans with chronic PTSD, resting and stress-induced levels of NPY have been reported as low compared with controls (Rasmusson et al., 2000). When the SNS is stressed or provoked in veterans with PTSD, they also experience an increase in NE, but the accompanying release of NPY appears insufficient to hold rising levels of

Published by:

The National Center for PTSD  
VA Medical and Regional  
Office Center (116D)  
215 North Main Street  
White River Junction  
Vermont 05009-0001 USA

(802) 296-5132

FAX (802) 296-5135

Email: [ptsd@dartmouth.edu](mailto:ptsd@dartmouth.edu)  
<http://www.ncptsd.org>

Subscriptions are available  
from the Superintendent of  
Documents, P.O. Box 371954,  
Pittsburgh, PA 15250-7954.

#### Editorial Director

Matthew J. Friedman,  
MD, PhD

#### Scientific Editor

Paula P. Schnurr, PhD

#### Managing Editor

Fred Lerner, DLS

#### Production Manager

Peggy Willoughby

#### Circulation Manager

Sandra Mariotti

#### In this issue:

- Emerging Neurobiological Factors in Stress Resilience
- PILOTS Pull-Out Guide

#### National Center Divisions

Executive  
White River Jct VT 05009

Behavioral Science  
Boston MA 02130

Education  
Menlo Park CA 94304

Clinical Neurosciences  
West Haven CT 06516

Evaluation  
West Haven CT 06516

Pacific Islands  
Honolulu HI 96813

Women's Health Sciences  
Boston MA 02130



<sup>1,2,4</sup> Authors' Address: Clinical Neurosciences Division, Psychiatry Service (116A), VA Medical Center, 950 Campbell Avenue, West Haven, CT 06516.

<sup>3,5</sup> Authors' Address: National Institute of Mental Health, 15K North Drive, Room 101, Bethesda, MD 20892-2670.

Authors' Email Addresses: <sup>1</sup> [Steven.Southwick@med.va.gov](mailto:Steven.Southwick@med.va.gov)

<sup>2</sup> [Charles.A.Morgan@yale.edu](mailto:Charles.A.Morgan@yale.edu) <sup>3</sup> [Meena.Vythi@nih.gov](mailto:Meena.Vythi@nih.gov)

<sup>4</sup> [John.Krystal@med.va.gov](mailto:John.Krystal@med.va.gov) <sup>5</sup> [Charneyd@nih.gov](mailto:Charneyd@nih.gov)

norepinephrine in check. Rapid increases in NE likely contribute to exaggerated increases in heart rate, blood pressure, respiratory rate, anxiety, panic, vigilance, and even intrusive combat-related memories (Southwick et al., 1999). Thus, NPY appears to be a neurobiological resilience factor that helps to maintain SNS reactivity at an optimal level. NPY has been shown to have anxiolytic effects in animals (Heilig et al., 1994) and antidepressant drugs have been shown to increase NPY in depressed patients with low levels of NPY (Husum & Mathé, 2002).

Galanin is a peptide that is involved in pain control, cardiovascular regulation, food intake, neuroendocrine control, learning and memory, and anxiety. A high percentage of noradrenergic neurons in the locus coeruleus co-express galanin. Galanin is preferentially released under conditions of high NE activity and reduces firing rate of the locus coeruleus. In rats, central administration of galanin modulates anxiety-related behaviors and when injected directly into the amygdala blocks the anxiogenic effects of stress, which is associated with increased NE release in the amygdala (Bing et al., 1993; Moller et al., 1999). Thus, like NPY, galanin appears to modulate the behavioral effects of stress-induced increases in NE with the overall net behavioral effects of NE hyperactivity depending on the balance between NE, NPY, and galanin (Charney, in press).

Like the SNS, the hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the stress response. Stress stimulates the release of corticotrophin-releasing hormone (CRH), which then activates adrenocorticotrophic hormone (ACTH). ACTH, in turn, increases the release of cortisol and dehydroepiandrosterone (DHEA). Cortisol mobilizes energy stores and increases arousal, vigilance, selective attention, and consolidation of memory. Cortisol also inhibits growth, contains the immune response and has regulatory effects on brain regions important to the stress response (Yehuda, 2003). Chronically elevated cerebrospinal fluid CRH has been linked with both major depression and PTSD in humans, and extreme elevations of cortisol in animals can have toxic effects on the body and brain, including neural degeneration in the hippocampus, a structure that is involved in learning and memory (Bremner et al., 1999). DHEA, which is secreted in conjunction with cortisol, helps to modulate the effects of cortisol and thus, under conditions of extreme stress, may serve a protective role (Kimonides et al., 1998).

It has been suggested that the capacity to restrain initial and chronic CRH responses to stress may be associated with psychobiological resilience and that DHEA may limit the toxic effects of excess stress-induced cortisol (Charney, in press). Regulation of the relative contribution of CRH-1 and CRH-2 receptors may also be important in modulating physiological and psychological responses to stress (Bale et al., 2002). It is possible that the administration of CRF antagonists and/or DHEA under conditions of high stress might increase psychobiological resilience in some individuals (Friedman, 2002).

Other likely neurobiological mediators of stress resilience include serotonin, dopamine, benzodiazepine receptor

binding, testosterone, and estrogen (Caspi et al., 2003; Charney, in press; Hariri et al., 2002; Morgan, Wang, Mason et al., 2000; Suay et al., 1999). For example, in recent studies, variations in the serotonin transporter gene have been associated with abnormal levels of anxiety, a propensity to become conditioned to fear, variations in brain responses to emotional stimuli, and likelihood of developing depression in response to life stress (Caspi et al., 2003; Hariri et al., 2002). Cortical alterations in benzodiazepine receptor binding have been found in chronically stressed animals and humans with excessive fear and anxiety-related behaviors and symptoms. Gamma-aminobutyric acid (GABA)-benzodiazepine receptor density and function may play an important role in stress resilience and vulnerability (Nutt & Malizia, 2001). Estrogen appears to have a beneficial effect in the short term by blunting HPA-axis and noradrenergic responses to stress (Komesaroff et al., 1999); however, long-term elevations of estrogen caused by chronic stress may enhance HPA-axis responses. It has been suggested that increased sensitivity to stress in women may, in part, be related to differences in stress-related gonadal steroid levels and function.

The above potential mediators of stress vulnerability and resilience, by themselves, may have insignificant or modest effects on health. However, the additive effect of dysregulations in multiple neurobiological systems on health may be substantial (Charney, in press; Friedman, 2002). This concept follows from the work of McEwen and Stellar (Karlman et al., 2002; McEwen & Stellar, 1993; Seeman et al., 2001), who described allostatic load as a cumulative measure of physiologic dysregulation in multiple systems. In a study measuring 10 biological markers of physiologic regulation, such as serum DHEA level, average systolic blood pressure, and 12-hour overnight urinary excretion of epinephrine, Seeman et al. (2001) found that none of the 10 markers on their own predicted a decline in health status. However, when all 10 markers were summarized together in a measure of allostatic load, they did successfully predict measures of health outcome, including new cardiovascular events and cognitive decline. Applying this model, resilient individuals may be those with relatively high stress-induced NPY, galanin, DHEA, and testosterone, and relatively low CRH and low HPA-axis and LC/NE activation. In contrast, vulnerable individuals may be more likely to achieve relatively high stress-induced increases in estrogen, dopamine, and HPA-axis and locus coeruleus (LC)/NE activation as well as relatively low stress-induced NPY, galanin, DHEA, and testosterone (Charney, in press). Clearly, numerous other mediators of the stress response, such as glutamate and neurotrophic factors, have an impact on stress vulnerability and resilience.

Neural pathways in the brain that regulate reward, motivation, learning, memory, responses to fear, and adaptive social behaviors also undoubtedly play a central role in mediating stress vulnerability or resilience, possibly through their relationship to relevant character traits. For example, it is possible that resilient individuals are able to

maintain optimism, hopefulness, and a positive self-concept when exposed to chronic stress, abuse, neglect, and an unrewarding environment because their neural reward and motivation pathways continue to function well even under harsh circumstances (Charney, in press). Similarly, optimal functioning of neural reward and motivation pathways may enhance other behaviors associated with resilience, such as the ability to bond with a group of individuals, to attract and use support from others, and to engage in altruistic behavior (Charney, in press; Masten & Coatsworth, 1998). Functional interactions among glutamate, NMDA receptors, dopamine, and dopamine receptors greatly influence optimal functioning of reward circuits. Genetic and/or environmentally induced abnormalities in these functional interactions could facilitate vulnerability or resistance to anhedonia and hopelessness in the face of stress (Charney, in press; Lenox et al., 2002).

Neural pathways involved in fear conditioning, consolidation of memory, reconsolidation of memory, and extinction are also likely involved in stress vulnerability and resilience. These regions have all been implicated in the pathophysiology of PTSD (Bremner et al., 1999). It has been hypothesized that stress-resilient individuals, compared to those who are stress-vulnerable, are less likely to over-consolidate emotional memories and less likely to over-generalize specific conditioned stimuli to a larger context. Such individuals are also likely to have greater capacity to reorganize existing emotional memories and to extinguish traumatic memories (Charney, in press).

It is unlikely that resilience can be explained by a single neurotransmitter, neuropeptide, hormone, or neural pathway. Instead, stress-resilient individuals probably possess numerous neurobiological mediators of hardiness. Future attempts to predict resilience will require the measurement of multiple neurobiological factors that can be assembled into a profile that characterizes individuals who are stress-vulnerable compared to those who are stress-resilient. Of course, genetic factors undoubtedly play a central role in stress vulnerability and resilience. It has been estimated that inherited factors contribute up to 32% of the variance of PTSD symptoms above and beyond the contribution of trauma severity (True et al., 1993). It is likely that genetic variability in a number of neurotransmitters, neuropeptides, hormones, and neural circuits already discussed in relation to resilience play a critical role in stress vulnerability and stress resilience.

It is hoped that a neurobiological understanding of resilience will lead to prevention and/or improved treatment of stress-related disorders such as PTSD. For example, we hypothesize that taking NPY, particularly for individuals who do not naturally release sufficient amounts, would boost physiological resilience during times of stress. Similarly, the prescription of other potential neurobiological mediators of resilience, such as DHEA or testosterone, might improve hardiness in many people. Currently available psychiatric medications, such as antidepressants and adrenergic blockers, may also have a role in facilitating resilience. Antidepressants have been shown to protect

against the effects of stress in animals and to stimulate the re-growth of hippocampal neurons (critical for learning and memory) that have been damaged by stress. Anti-adrenergic agents, like propranolol, when given immediately after a traumatic event may prevent over-consolidation of fear-related memories and thus prevent the development of PTSD (Pitman et al., 2002; Southwick et al., 1999). Further, some forms of psychotherapy and social support may serve to bolster extinction of the fear-conditioned memories and cortical inhibition of limbic hyper-responsivity so commonly seen in individuals with anxiety disorders.

Currently the National Center for PTSD is conducting a number of exciting projects related to the neurobiology of resilience. Dr. Charles A. Morgan III is leading a team of investigators that is studying neurochemical and physiological responses to high-intensity military training stress and relating these responses to resilience, vulnerability, memory, and performance. The Center is also collaborating with the National Institute of Mental Health's Mood and Anxiety Disorders Program headed by Dr. Dennis Charney. In this collaboration, Drs. Meena Vythilingam and Dennis Charney of the NIMH and Dr. Southwick of the National Center are conducting a comprehensive study of resilience among former prisoners of war, combat medal winners, and active-duty Special Forces soldiers. Neural circuits mediating fear, reward, social cooperation, memory, and emotion regulation are being studied using functional magnetic resonance imaging. Relationships and interactions among these neural circuits are being correlated with clinical, neuroendocrine, and neuropsychological findings. It is anticipated that identification of biological and psychosocial factors related to resilience could help to predict vulnerability to stress-related illness following traumatic exposure and facilitate the development of treatments to enhance resilience.

## REFERENCES

- BREMNER, J.D., SOUTHWICK, S.M., & CHARNEY, D.S. (1999). **The neurobiology of posttraumatic stress disorder: An integration of animal and human research.** In P.A. Saigh & J.D. Bremner (Eds.), *Posttraumatic stress disorder: A comprehensive text* (pp. 103-143). Boston: Allyn & Bacon.
- SOUTHWICK, S.M., BREMNER, J.D., RASMUSSEN, A., MORGAN, C.A., ARNSTEN, A., & CHARNEY, D.S. (1999). **Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder.** *Biological Psychiatry*, 46, 1192-1204.
- TRUE, W.R., RICE, J., EISEN, S.A., HEATH, A.C., GOLDBERG, J., LYONS, M.J., & NOWAK, J. (1993). **A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms.** *Archives of General Psychiatry*, 50, 257-264.
- YEHUDA, R. (2003). **Adult neuroendocrine aspects of PTSD.** *Psychiatric Annals*, 33, 30-36.



## SELECTED ABSTRACTS

BING, O., MÖLLER, C., ENGEL, J.A., SÖDERPALM, B., & HEILIG, M. (1993). **Anxiolytic-like action of centrally administered galanin.** *Neuroscience Letters*, 164, 17-20. The neuropeptide galanin is present in limbic brain areas important for emotionality. We examined whether central galanin may be involved in mechanisms of anxiety. Rats were tested in a pharmacologically validated animal model of anxiety, the Vogel punished drinking test. A 100% increase of punished responding was seen after 3 nmol galanin i.c.v. After 15 nmol, signs of sedation were seen, and no increase of punished responding could be observed. Drinking motivation, shock thresholds and exploratory locomotor activity were not affected by 3 nmol galanin. These results support a specific anxiolytic-like action of galanin, similar to that of the functionally related peptide, neuropeptide Y.

CASPI, A., SUGDEN, K., MOFFITT, T.E., TAYLOR, A., CRAIG, I.W., HARRINGTON, H., MCCLAY, J., MILL, J., MARTIN, J., BRAITHWAITE, A., & POULTON, R. (2003). **Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene.** *Science*, 301, 386-389. In a prospective-longitudinal study of a representative birth cohort, we tested why stressful experiences lead to depression in some people but not in others. A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

CHARNEY, D.S. (in press). **Psychobiological mechanisms of resilience and vulnerability: Implications for the successful adaptation to extreme stress.** *American Journal of Psychiatry*. *Objective:* Most research on the effects of severe psychological stress has focused on stress related psychopathology. Here, the author develops psychobiological models of resilience to extreme stress. *Method:* An integrative model of resilience and vulnerability that encompasses the neurochemical response patterns to acute stress and the neural mechanisms mediating reward, fear conditioning and extinction, and social behavior is proposed. *Results:* Eleven possible neurochemical, neuropeptide, and hormonal mediators of the psychobiological response to extreme stress were identified and related to resilience or vulnerability. The neural mechanisms of reward and motivation (hedonia, optimism, learned helpfulness), fear responsiveness (effective behaviors despite fear) and adaptive social behavior (altruism, bonding, teamwork) were found to be relevant to the character traits associated with resilience. *Conclusions:* The opportunity now exists to bring to bear the full power of advances in our understanding of the neurobiological basis of behavior to facilitate the discoveries needed to predict, prevent, and treat stress related psychopathology.

CHARNEY, D.S. (2003). **The psychobiology of resilience and vulnerability to anxiety disorders: Implications for prevention and treatment.** *Dialogues in Clinical Neuroscience*, 5, 207-221. Much of the research on the neurobiology of human anxiety disorders has focused on psychopathological abnormalities in patients with anxiety disorders. While this line of research is

obviously important, more investigation is needed to elucidate the psychobiology of resilience to extreme stress. Study of the psychobiology of resilience has the potential to identify neurochemical, neuropeptide, and hormonal mediators of vulnerability and resilience to severe stress. In addition, the relevance of neural mechanisms of reward and motivation, fear responsiveness, and social behavior to character traits associated with risk and resistance to anxiety disorders may be clarified. These areas of investigation should lead to improved methods of diagnosis, novel approaches to prevention, and new targets for antianxiety drug discovery.

DIENSTBIER, R.A. (1989). **Arousal and physiological toughness: Implications for mental and physical health.** *Psychological Review*, 96, 84-100. From W. B. Cannon's identification of adrenaline with "fight or flight" to modern views of stress, negative views of peripheral physiological arousal predominate. Sympathetic nervous system (SNS) arousal is associated with anxiety, neuroticism, the Type A personality, cardiovascular disease, and immune system suppression; illness susceptibility is associated with life events requiring adjustments. "Stress control" has become almost synonymous with arousal reduction. A contrary positive view of peripheral arousal follows from studies of subjects exposed to intermittent stressors. Such exposure leads to low SNS arousal base rates, but to strong and responsive challenge- or stress-induced SNS-adrenal-medullary arousal, with resistance to brain catecholamine depletion and with suppression of pituitary adrenal-cortical responses. That pattern of arousal defines physiological toughness and, in interaction with psychological coping, corresponds with positive performance in even complex tasks, with emotional stability, and with immune system enhancement.

FRIEDMAN, M.J. (2002). **Future pharmacotherapy for post-traumatic stress disorder: Prevention and treatment.** *Psychiatric Clinics of North America*, 25, 427-441. I have presented two complementary lines of speculation in this article. First, I have presented a public health model of resilience, prevention, acute intervention, and tertiary treatment to inform a pharmacotherapeutic strategy for PTSD in the future. Second, I have proposed a rational rather than an empirical approach to the clinical pharmacology of PTSD. Such an approach suggests that efforts be directed toward the development and testing of new classes of drugs designed to target the unique pathophysiology of PTSD. [Text, p. 438]

HARIRI, A.R., MATTAY, V.S., TESSITORE, A., KOLACHANA, B., FERA, F., GOLDMAN, D., EGAN, M.F., & WEINBERGER, D.R. (2002). **Serotonin transporter genetic variation and the response of the human amygdala.** *Science*, 297, 400-403. A functional polymorphism in the promoter region of the human serotonin transporter gene (SLC6A4) has been associated with several dimensions of neuroticism and psychopathology, especially anxiety traits, but the predictive value of this genotype against these complex behaviors has been inconsistent. Serotonin [5-hydroxytryptamine, (5-HT)] function influences normal fear as well as pathological anxiety, behaviors critically dependent on the amygdala in animal models and in clinical studies. We now report that individuals with one or two copies of the short allele of the serotonin transporter (5-HTT) promoter polymorphism, which has been associated with reduced 5-HTT expression and function and increased fear and anxiety-related behaviors, exhibit greater amygdala neuronal activity, as assessed by BOLD functional magnetic resonance imaging, in response to fearful

stimuli compared with individuals homozygous for the long allele. These results demonstrate genetically driven variation in the response of brain regions underlying human emotional behavior and suggest that differential excitability of the amygdala to emotional stimuli may contribute to the increased fear and anxiety typically associated with the short SLC6A4 allele.

HUSUM, H. & MATHÉ, A.A. (2002). **Early life stress changes concentrations of neuropeptide Y and corticotropin-releasing hormone in adult rat brain. Lithium treatment modifies these changes.** *Neuropsychopharmacology*, 27, 756-764. Experiences of early life stress are more prevalent among depressed patients than healthy controls. Neuropeptide Y (NPY) was suggested to play a role in the pathophysiology of depression. Consequently, we investigated in adult rats the effects of maternal deprivation for 3 h/day during postnatal days (PND) 2-14 and of dietary lithium during PND 50-83 on brain levels of NPY-like immunoreactivity (LI). Brain levels of corticotropin-releasing hormone (CRH) and serum corticosterone were also measured. Maternal deprivation reduced NPY-LI levels in the hippocampus and the striatum but increased NPY-LI and CRH-LI levels in the hypothalamus. Lithium treatment counteracted the effect of maternal deprivation in the hippocampus and striatum by increasing NPY-LI levels. In the hypothalamus, lithium tended to decrease CRH-LI but further increased levels of NPY-LI; it also increased serum corticosterone levels. The results suggest that early life stress has long-term effects on brain NPY with implications for the development of depression/vulnerability to stress, and that one therapeutic mechanism of action of lithium is to increase brain NPY.

KARLAMANGLA, A.S., SINGER, B.H., MCEWEN, B.S., ROWE, J.W., & SEEMAN, T.E. (2002). **Allostatic load as a predictor of functional decline: MacArthur studies of successful aging.** *Journal of Clinical Epidemiology*, 55, 696-710. Allostatic load has been proposed as a cumulative measure of dysregulation across multiple physiological systems, and has been postulated to impact health risks. In the allostatic load model, increased risk is hypothesized to result not only from large and clinically significant dysregulation in individual systems, but also from more modest dysregulation, if present in multiple systems. Our objective was to construct an allostatic load score by optimally combining several physiologic measurements, and to examine its association with future functional decline. We analyzed data from a 7-year longitudinal study of a community-based cohort, whose age at baseline was between 70 and 79 years. Canonical correlation analysis was used to study the association of 10 biological measurements representing allostatic load with declines in scores on five tests each of physical and cognitive function over two follow-up periods: 1998-1991 and 1991-1995. We used bootstrapping to evaluate the stability of the canonical correlation and canonical weights. The canonical correlation between allostatic load and the 20 decline scores was 0.43 ( $p = .03$ ) and the [25th, 75th] percentile interval of its distribution over 200 bootstrapped subsamples of the cohort was [0.48, 0.53]. These findings were not substantially affected by adjusting for covariates and cardiovascular disease. We conclude that a summary measure of physiologic dysregulation, such as allostatic load, is an independent predictor of functional decline in elderly men and women.

KIMONIDES, V.G., KHATIBI, N.H., SVENDSEN, C.N., SOFRONIEW, M.V., & HERBERT, J. (1998). **Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS)**

**protect hippocampal neurons against excitatory amino acid-induced neurotoxicity.** *Proceedings of the National Academy of Sciences of the United States of America*, 95, 1852-1857. DHEA, together with DHEAS, is the most abundant steroid in the blood of young adult humans. Levels in humans decline with age and during certain types of illness or stress. We have found that DHEA(S) can prevent or reduce the neurotoxic actions in the hippocampus of the glutamate agonists N-methyl-D-aspartic acid (NMDA) both in vitro and in vivo or alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid in vitro. Pre-treatment with DHEA (10-100 nM for 6-8 h) protected primary hippocampal cultures from embryonic day 18 (E18) embryos against NMDA-induced toxicity (0.1, 1, 10, and 50 mM). DHEA added either with NMDA (1 mM) or 1 h later had lesser, but still significant, protective actions. DHEAS also reduced NMDA-induced toxicity (1 mM), although the lowest effective dose of DHEAS (100 nM) was higher than that of DHEA (10 nM). DHEA (100 nM) protected cultured neurons against the neurotoxic actions of either AMPA (25 microM) or kainic acid (1 mM) as well. In vivo, s.c. pellets of DHEA, which resulted in plasma levels that resembled those in young adult humans, protected hippocampal CA1/2 neurons against unilateral infusions of 5 or 10 nmol of NMDA. Because the release of glutamate has been implicated in the neural damage after cerebral ischemia and other neural insults, these results suggest that decreased DHEA levels may contribute significantly to the increased vulnerability of the aging or stressed human brain to such damage.

KOMESAROFF, P.A., ESLER, M.D., & SUDHIR, K. (1999). **Estrogen supplementation attenuates glucocorticoid and catecholamine responses to mental stress in perimenopausal women.** *Journal of Clinical Endocrinology and Metabolism*, 84, 606-610. Estrogens are reported to provide protection against the development of cardiovascular disease in women, but the mechanisms underlying these effects are not well defined. We hypothesized that estrogen might affect the hormonal responses to stress. We therefore studied cortisol, ACTH, epinephrine, norepinephrine, and norepinephrine spillover and hemodynamic responses to a 10-min mental arithmetic test in 12 perimenopausal women randomized to 8 weeks of estrogen supplementation (estradiol valerate, 2 mg daily;  $n = 7$ ) or placebo ( $n = 5$ ). Total body and forearm norepinephrine spillover were measured by radiotracer methodology. After supplementation with estradiol, the increases in both systolic and diastolic blood pressure in response to mental stress were reduced, and cortisol, ACTH, plasma epinephrine and norepinephrine, and total body norepinephrine spillover responses to stress were significantly attenuated ( $P < 0.05$  in each case). Forearm norepinephrine spillover was unchanged by estrogen, and there was no change in any of the responses after placebo. We conclude that estrogen supplementation in perimenopausal women attenuates blood pressure, glucocorticoid, and catecholamine responses to psychological stress.

LENOX, R.H., GOULD, T.D., & MANJI, H.K. (2002). **Endophenotypes in bipolar disorder.** *American Journal of Medical Genetics*, 114, 391-406. The search for genes in bipolar disorder has provided numerous genetic loci that have been linked to susceptibility to developing the disorder. However, because of the genetic heterogeneity inherent in bipolar disorder, additional strategies may need to be employed to fully dissect the genetic underpinnings. One such strategy involves reducing complex behaviors into their component parts (endophenotypes). Abnormal neurophysiological, biochemical, endocrinological, neuroana-

tomical, cognitive, and neuropsychological findings are characteristics that often accompany psychiatric illness. It is possible that some of these may eventually be useful in subdefining complex genetic disorders, allowing for improvements in diagnostic assessment, genetic linkage studies, and development of animal models. Findings in patients with bipolar disorder that may eventually be useful as endophenotypes include abnormal regulation of circadian rhythms (the sleep/wake cycle, hormonal rhythms, etc.), response to sleep deprivation, P300 event-related potentials, behavioral responses to psychostimulants and other medications, response to cholinergics, increase in white matter hyperintensities (WHIs), and biochemical observations in peripheral mononuclear cells. Targeting circadian rhythm abnormalities may be a particularly useful strategy because circadian cycles appear to be an inherent evolutionarily conserved function in all organisms and have been implicated in the pathophysiology of bipolar disorder. Furthermore, lithium has been shown to regulate circadian cycles in diverse species, including humans, possibly through inhibition of glycogen synthase kinase 3-beta (GSK-3beta), a known target of lithium.

MASTEN, A.S. & COATSWORTH, J.D. (1998). **The development of competence in favorable and unfavorable environments: Lessons from research on successful children.** *American Psychologist*, 53, 205-220. The development of competence holds great interest for parents and society alike. This article considers implications from research on competence and resilience in children and adolescents for policy and interventions designed to foster better outcomes among children at risk. Foundations of competence in early development are discussed, focusing on the role of attachment relationships and self-regulation. Results from studies of competence in the domains of peer relations, conduct, school, work, and activities are highlighted. Lessons are drawn from studies of naturally occurring resilience among children at risk because of disadvantage or trauma and also from efforts to deliberately alter the course of competence through early childhood education and preventive interventions. Converging evidence suggests that the same powerful adaptive systems protect development in both favorable and unfavorable environments.

MCEWEN, B.S. & STELLAR, E. (1993). **Stress and the individual: Mechanisms leading to disease.** *Archives of Internal Medicine*, 153, 2093-2101. *Data Synthesis:* Stress is frequently seen as a significant contributor to disease, and clinical evidence is mounting for specific effects of stress on immune and cardiovascular systems. Yet, until recently, aspects of stress that precipitate disease have been obscure. The concept of homeostasis has failed to help us understand the hidden toll of chronic stress on the body. Rather than maintaining constancy, the physiologic systems within the body fluctuate to meet demands from external forces, a state termed allostasis. In this article, we extend the concept of allostasis over the dimension of time and we define allostatic load as the cost of chronic exposure to fluctuating or heightened neural or neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful. [Adapted from Author Abstract]

MÖLLER, C., SOMMER, W., THORSELL, A., & HEILIG, M. (1999). **Anxiogenic-like action of galanin after intra-amygdala administration in the rat.** *Neuropsychopharmacology*, 21, 507-512. The neuropeptide galanin is expressed in brain structures implicated in regulation of emotionality. The amygdala is known to play a central role in mechanisms of fear and anxiety. We

therefore examined the effects of galanin (0.2 and 0.6 nmol/side) on experimental anxiety upon microinjection into the amygdala. Two established animal models of anxiety were used: a punished drinking test, and the elevated plus-maze. Punished responding was dose dependently suppressed by intra-amygdala galanin, whereas unpunished responding, drinking motivation, locomotor activity, and shock thresholds were unaffected. No effects on experimental anxiety were seen in the plus-maze following galanin injection. When injected into parietal cortex, no anxiety promoting properties of galanin were detected. These data suggest that activation of galanin receptors in amygdala modulates neurotransmission involved in fear and experimental anxiety.

MORGAN, C.A., WANG, S., MASON, J., SOUTHWICK, S.M., FOX, P., HAZLETT, G., CHARNEY, D.S., & GREENFIELD, G. (2000). **Hormone profiles in humans experiencing military survival training.** *Biological Psychiatry*, 47, 891-901. *Background:* Clinical models of the human response to intense, acute stress have been limited to laboratory settings or cross sectional characterizations. As a result, data about the sensitivity of the human neuroendocrine activation to realistic stressors of varying magnitudes are limited. The U.S. Army survival course offers a unique opportunity to examine, in a controlled manner, the human response to acute, realistic, military stress. *Methods:* Salivary data were collected in 109 subjects at baseline during four stress exposure time points and at recovery. Serum data was collected at baseline and recovery in 72 subjects and at baseline and during stress exposure in a subgroup of subjects ( $n = 21$ ). *Results:* Cortisol significantly increased during the captivity experience and was greatest after subjects' exposure to interrogations. Cortisol remained significantly elevated at recovery. Testosterone was significantly reduced within 12 hours of captivity. Reductions of both total and free T4 and of total and free T3 were observed, as were increases in thyrotropin. *Conclusions:* The stress of military survival training produced dramatic alterations in cortisol, percent free cortisol, testosterone, and thyroid indices. Different types of stressors had varying effects on the neuroendocrine indices. The degree of neuroendocrine changes observed may have significant implications for subsequent responses to stress.

MORGAN, C.A., WANG, S., SOUTHWICK, S.M., RASMUSSEN, A., HAZLETT, G., HAUGER, R.L., & CHARNEY, D.S. (2000). **Plasma neuropeptide-Y concentrations in humans exposed to military survival training.** *Biological Psychiatry*, 47, 902-909. *Background:* Neuropeptide-Y (NPY) is present in extensive neuronal systems of the brain and is present in high concentrations in cell bodies and terminals in the amygdala. Preclinical studies have shown that injections of NPY into the central nucleus of the amygdala function as a central anxiolytic and buffer against the effects of stress. The objective of this study was to assess plasma NPY immunoreactivity in healthy soldiers participating in high intensity military training at the U.S. Army survival school. The Army survival school provides a means of observing individuals under high levels of physical, environmental, and psychological stress, and consequently is considered a reasonable analogue to stress incurred as a result of war or other catastrophic experiences. *Methods:* Plasma levels of NPY were assessed at baseline (prior to initiation of training), and 24 hours after the conclusion of survival training in 49 subjects, and at baseline and during the Prisoner of War (P.O.W) experience (immediately after exposure to a military interrogation) in 21 additional subjects. *Results:* Plasma NPY levels were significantly increased compared to baseline following interrogations and were significantly higher in Special Forces soldiers, compared to non-Special Forces soldiers. NPY elicited by interrogation stress was significantly



correlated to the subjects' behavior during interrogations and tended so be negatively correlated to symptoms of reported dissociation. 24 hours after the conclusion of survival training, NPY had returned to baseline in Special Forces soldiers, but remained significantly lower than baseline values in non-Special Forces soldiers. NPY was positively correlated with both cortisol and behavioral performance under stress. NPY was negatively related to psychological symptoms of dissociation. *Conclusions:* These results provide evidence that uncontrollable stress significantly increases plasma NPY in humans, and when extended, produces a significant depletion of plasma NPY. Stress-induced alterations of plasma NPY were significantly different in Special Forces soldiers compared to non-Special Forces soldiers. These data support the idea that NPY may be involved in the enhanced stress resilience seen in humans.

NUTT, D.J. & MALIZIA, A.L. (2001). **New insights into the role of the GABA<sub>A</sub>-benzodiazepine receptor in psychiatric disorder.** *British Journal of Psychiatry*, 179, 390-396. *Background:* In the 40 years since the first benzodiazepine was brought into clinical use there has been a substantial growth in understanding the molecular basis of action of these drugs and the role of their receptors in disease states. *Aims:* To present current knowledge about the role of the GABA<sub>A</sub>-benzodiazepine receptor in anxiety disorders, new insights into the molecular biology of the receptor complex and neuroimaging studies suggesting involvement of these receptors in disease states. *Method:* An overview of published literature, including some recent data. *Results:* The molecular biology of this receptor is detailed. Molecular genetic studies suggesting involvement of the GABA<sub>A</sub>-benzodiazepine receptor in animal behaviour and learning are outlined; possible parallels with human psychopathology are discussed. *Conclusions:* Current insights into the role of the GABA<sub>A</sub>-benzodiazepine receptor in the action of benzodiazepines and as a factor in disease states, in both animals and humans, may lead to new, more sophisticated interventions at this receptor complex and potentially significant therapeutic gains.

PITMAN, R.K., SANDERS, K.M., ZUSMAN, R.M., HEALY, A.R., CHEEMA, F., LASKO, N.B., CAHILL, L., & ORR, S.P. (2002). **Pilot study of secondary prevention of posttraumatic stress disorder with propranolol.** *Biological Psychiatry*, 51, 189-192. *Background:* Preclinical considerations suggest that treatment with a beta-adrenergic blocker following an acute psychologically traumatic event may reduce subsequent PTSD symptoms. This pilot study addressed this hypothesis. *Methods:* Patients were randomized to begin, within 6 hours of the event, a 10-day course of double-blind propranolol ( $n = 18$ ) versus placebo ( $n = 23$ ) 40 mg four times daily. *Results:* The mean (SD) 1-month Clinician-Administered PTSD Scale (CAPS) score of 11 propranolol completers was 27.6 (15.7), with one outlier 5.2 SDs above the others' mean, and of 20 placebo completers, 35.5 (21.5),  $t = 1.1$ ,  $df = 29$ ,  $p = .15$ . 2 propranolol patients' scores fell above, and 9 below, the placebo group's median,  $p = .03$  (sign test). 0 of 8 propranolol, but 6 of 14 placebo, patients were physiologic responders during script-driven imagery of the traumatic event when tested 3 months afterward,  $p = .04$  (all  $p$  values one-tailed). *Conclusion:* These pilot results suggest that acute, post-trauma propranolol may have a preventive effect on subsequent PTSD.

RASMUSSEN, A.M., HAUGER, R.L., MORGAN, C.A., BREMNER, J.D., CHARNEY, D.S., & SOUTHWICK, S.M. (2000). **Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD.** *Biological Psychiatry*, 47, 526-539. *Background:* Consistent with many studies demonstrat-

ing enhanced reactivity of the sympathetic nervous system in PTSD, the administration of yohimbine, a noradrenergic alpha(2)-antagonist, has been shown to increase core symptoms of PTSD and to induce greater increases in plasma 3-methyl-4-hydroxy-phenyl-glycol (MHPG) in subjects with PTSD compared with healthy control subjects. In turn, neuropeptide Y (NPY) has been shown to inhibit the release of norepinephrine from sympathetic noradrenergic neurons. *Methods:* In the following study, plasma NPY responses to yohimbine and placebo were measured in a subgroup of 18 subjects with PTSD and 8 healthy control subjects who participated in the previous study of the effect of yohimbine on plasma MHPG. *Results:* The PTSD subjects had lower baseline plasma NPY and blunted yohimbine-stimulated increases in plasma NPY compared with the healthy control subjects. Within the PTSD group, baseline plasma NPY levels correlated negatively with combat exposure scale scores, baseline PTSD and panic symptoms, and yohimbine-stimulated increases in MHPG and systolic blood pressure. *Conclusions:* This study suggests that combat stress-induced decreases in plasma NPY may mediate, in part, the noradrenergic system hyperreactivity observed in combat-related PTSD. The persistence of this decrease in plasma NPY may contribute to symptoms of hyperarousal and the expression of exaggerated alarm reactions, anxiety reactions, or both in combat veterans with PTSD long after war.

SEEMAN, T.E., MCEWEN, B.S., ROWE, J.W., & SINGER, B.H. (2001). **Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging.** *Proceedings of the National Academy of Sciences of the United States of America*, 98, 4470-4475. Allostatic load (AL) has been proposed as a new conceptualization of cumulative biological burden exacted on the body through attempts to adapt to life's demands. Using a multisystem summary measure of AL, we evaluated its capacity to predict four categories of health outcomes, 7 years after a baseline survey of 1,189 men and women age 70-79. Higher baseline AL scores were associated with significantly increased risk for 7-year mortality as well as declines in cognitive and physical functioning and were marginally associated with incident cardiovascular disease events, independent of standard socio-demographic characteristics and baseline health status. The summary AL measure was based on 10 parameters of biological functioning, four of which are primary mediators in the cascade from perceived challenges to downstream health outcomes. Six of the components are secondary mediators reflecting primarily components of the metabolic syndrome (syndrome X). AL was a better predictor of mortality and decline in physical functioning than either the syndrome X or primary mediator components alone. The findings support the concept of AL as a measure of cumulative biological burden.

## IMPORTANT NOTICE TO OUR VA SUBSCRIBERS:

### KEEP YOUR RESEARCH QUARTERLY COMING

If you are receiving a copy of the *PTSD Research Quarterly* personally addressed to you at your VA address, and the code 99 appears on the mailing label on your copy of this issue, you need to let us know that your address is correct and that you wish to continue receiving the *Research Quarterly*. To do this, just photocopy the mailing label on the back page and return it to us. If you need to correct your VA address, please print the new address next to the old one.

## ADDITIONAL CITATIONS

### Annotated by the Editor

BALE, T.L., PICETTI, R., CONTARINO, A., KOOB, G.F., VALE, W.W., & LEE, K-F. (2002). **Mice deficient for both corticotropin-releasing factor receptor 1 (CRFR1) and CRFR2 have an impaired stress response and display sexually dichotomous anxiety-like behavior.** *Journal of Neuroscience*, 22, 193-199.

Generated double-mutant mice that were deficient in both CRF receptor 1 and CRF receptor 2. The females displayed anxiolytic behavior, and the males displayed more anxious behavior than the females. Mutation in a mother also affected the behavior of pups.

HEILIG, M., KOOB, G.F., EKMAN, R., & BRITTON, K.T. (1994). **Corticotropin-releasing factor and neuropeptide Y: Role in emotional integration.** *Trends in Neuroscience*, 17, 80-85.

Reviewed information suggesting that CRF and NPY have reciprocal influences on the regulation of the stress response, possibly through the interaction of these systems in the amygdala.

INSEL, T.R. & YOUNG, L.J. (2001). **The neurobiology of attachment.** *Nature Reviews Neuroscience*, 2, 129-136.

Reviewed evidence about the neural basis of attachment at molecular, cellular, and systems levels. The authors suggest that neuropeptides that mediate attachment modulate fast neurotransmitters, have discrete CNS distributions, and are regulated by highly plastic receptors.

MARTINS, A.P., MARRAS, R.A., & GUIMARÃES, F.S. (2000). **Anxiolytic effect of a CRH receptor antagonist in the dorsal periaqueductal gray.** *Depression and Anxiety*, 12, 99-101.

Administered a CRF receptor antagonist, alpha-helical CRH9-41, to determine its anxiolytic effects on rats that were exposed to restraint stress and on unstressed control rats. As hypothesized, the compound had no effect on controls, but reversed the anxiogenic effect of restraint in the stressed animals.

MCGAUGH, J.L. & ROOZENDAAL, B. (2002). **Role of adrenal stress hormones in forming lasting memories in the brain.** *Current Opinion in Neurobiology*, 12, 205-210.

Reviewed evidence on how epinephrine and glucocorticoids modulate long-term memory consolidation in animals and hu-

mans. The authors conclude that release of NE and activation of b-adrenoreceptors in the amygdala are necessary in mediating the adrenal stress hormone regulation of memory consolidation.

MYERS, K.M. & DAVIS, M. (2001). **Behavioral and neural analysis of extinction.** *Neuron*, 36, 567-584.

Reviewed behavioral, cellular, and molecular evidence on extinction. The authors suggest that the most important research issue is the identification and characterization of which features are shared with acquisition and which are unique to inhibition.

SUAY, F., SALVADOR, A., GONZÁLEZ-BONO, E., SANCHÍS, C., MARTÍNEZ, M., MARTÍNEZ-SANCHÍS, S., SIMÓN, V.M., & MONTORO, J.B. (1999). **Effects of competition and its outcome on serum testosterone, cortisol and prolactin.** *Psychoneuroendocrinology*, 24, 551-566.

Assessed serum testosterone, cortisol, and prolactin in 26 male judo fighters during a judo fight, ergometric exercise, and a control session. Results varied by condition, and in the competition, by outcome. The neurohormonal changes were related to changes in psychological processes.

YOUNG, E.A., ALTEMUS, M., PARKISON, V., & SHASTRY, S. (2001). **Effects of estrogen antagonists and agonists on the ACTH response to restraint stress in female rats.** *Neuropsychopharmacology*, 25, 881-891.

Assessed the effects of two estrogen antagonists on ACTH and cortisol levels in female rats exposed to restraint stress. The authors also assessed the effects of estradiol and/or progesterone replacement on restraint stress in ovariectomized female rats. Findings suggest that estradiol inhibits the HPA response to stress in females.

YOUNG, L.J. (2002). **The neurobiology of social recognition, approach, and avoidance.** *Biological Psychiatry*, 51, 18-26.

Discusses rodent models of the neurobiology of the recognition of social stimuli, affiliative behavior, and social avoidance. The neuropeptides oxytocin and vasopressin appear to play important roles in modulating these behaviors.

National Center for PTSD (116D)  
VA Medical and Regional Office Center  
215 North Main Street  
White River Junction, Vermont 05009-0001

**Return Service Requested**

First Class Presort US Postage Paid Permit No 726 Concord, NH
---